Systemic Neutrophil Depletion Modulates the Migration and Fate of Transplanted Human Neural Stem Cells to Rescue Functional Repair.

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Public Summary:

Scientific Abstract:
The interaction of transplanted stem cells with local cellular and molecular cues in the host CNS microenvironment may affect the potential for repair by therapeutic cell populations. In this regard, spinal cord injury (SCI), Alzheimer's disease, and other neurological injuries and diseases all exhibit dramatic and dynamic changes to the host microenvironment over time. Previously, we reported that delayed transplantation of human CNS-derived neural stem cells (hCNS-SCns) at 9 or 30 d post-SCI (dpi) resulted in extensive donor cell migration, predominantly neuronal and oligodendrocytic donor cell differentiation, and functional locomotor improvements. Here, we report that acute transplantation of hCNS-SCns at 0 dpi resulted in localized astroglial differentiation of donor cells near the lesion epicenter and failure to produce functional improvement in an all-female immunodeficient mouse model. Critically, specific immunodepletion of neutrophils (polymorphonuclear leukocytes) blocked hCNS-SCns astroglial differentiation near the lesion epicenter and rescued the capacity of these cells to restore function. These data represent novel evidence that a host immune cell population can block the potential for functional repair derived from a therapeutic donor cell population, and support targeting the inflammatory microenvironment in combination with cell transplantation after SCI.SIGNIFICANCE STATEMENT The interaction of transplanted cells with local cellular and molecular cues in the host microenvironment is a key variable that may shape the translation of neurotransplantation research to the clinical spinal cord injury (SCI) human population, and few studies have investigated these events. We show that the specific immunodepletion of polymorphonuclear leukocyte neutrophils using anti-Ly6G inhibits donor cell astrogliosis and rescues the capacity of a donor cell population to promote locomotor improvement after SCI. Critically, our data demonstrate novel evidence that a specific host immune cell population can block the potential for functional repair derived from a therapeutic donor cell population.